

## PATENT ABSTRACTS OF JAPAN

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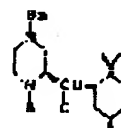
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## (54) PRODUCTION OF OPTICALLY ACTIVE PIPERAZINECARBOXYLIC ACID ESTER

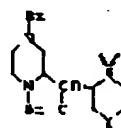
## (57) Abstract:

PROBLEM TO BE SOLVED: To produce the subject compound in high yield by heating the S-isomer or a solution consisting essentially of the S-isomer in the presence of a base, providing a mixture of the R- and the S-isomers and then optically resolving the resultant mixture.

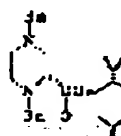
SOLUTION: L-Menthyl (S)-1,4-bis(phenylmethyl)-2-piperazinecarboxylate represented by formula I or a solution consisting essentially of the menthyl ester is heated in the presence of a base to provide a mixture of L-menthyl (R)-1,4-bis(phenylmethyl)-2-piperazinecarboxylate represented by formula II with the L-menthyl (S)-1,4-bis(phenylmethyl)-2-piperazinecarboxylate. The resultant mixture is then optically resolved to thereby produce L-menthyl (R)-1,4-bis(phenylmethyl)-2-piperazinecarboxylate represented by formula III. The compound represented by formula III is useful as an intermediate for (R)-4-(3-phosphono-2-propenyl)-2-piperazinecarboxylic acid represented by formula IV which is an excellent antidepressant and anti-Alzheimer disease agent.



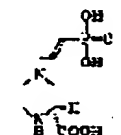
I



II



III



IV

## LEGAL STATUS

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## DETAILED DESCRIPTION

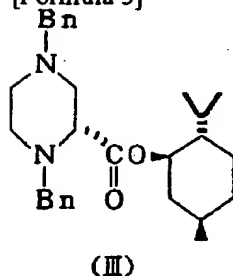
### [Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] this invention relates to the useful manufacture technique industrially [ (R)-1 of the optical activity shown by the formula (III), and 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester ]. The (R)-4-(3-phosphono-2-propenyl)-2-piperazine carboxylic acid shown by the formula (V) is outstanding anti-\*\*\*\* and anti-Alzheimer's-disease medicine (JP,63-203691,A) which were developed at the Switzerland sand company, and the compound expressed with a formula (III) is useful as intermediate field of (V).

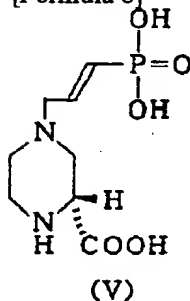
[0002]

[Formula 5]



[0003]

[Formula 6]

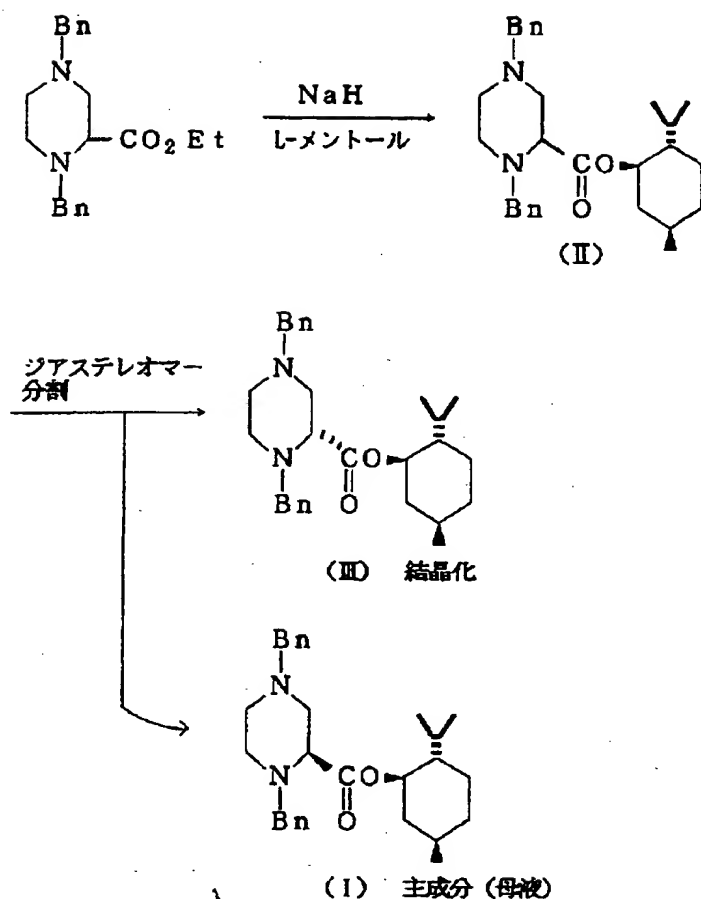


[0004]

[Description of the Prior Art] Conventionally, after the synthesis method of (R)-1 and 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester (R bodies) expressed with a formula (III) made the transesterification of 1 and 4-screw (phenyl methyl)-2-piperazine carboxylic-acid low-grade alkyl ester and L-menthol perform, according to the solubility difference of the obtained diastereomer compound, it divided the diastereomer and had obtained R bodies (III). At that time, (S)-1 expressed with the formula (I) which is the principal component of a mother liquor, and 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester (S bodies) became unnecessary, and yield was also low (JP,63-203691,A).

[0005]

[Formula 7]



[0006]

[Problem(s) to be Solved by the Invention] The development of the technique of reusing S bodies (I) which became unnecessary from the above thing was desired. this invention carries out racemization of the S unnecessary bodies (I), and is made into R and S mixture, and R bodies (III) are further taken out from the mixture, and it aims at measuring the enhancement in yield.

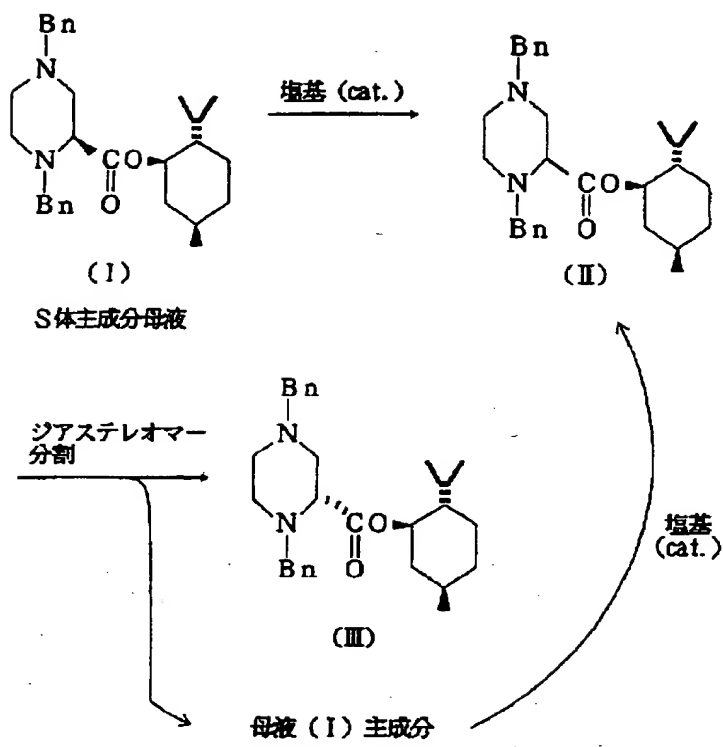
[0007]

[Means for Solving the Problem] This invention persons came to complete this invention, as a result of examining the above-mentioned technical problem.

[0008] That is, it is the manufacture technique of R bodies (III) characterized by carrying out optical resolution of it after this invention heats the solution which makes S bodies or S bodies a principal component under base presence and makes it R and S mixture (II).

[0009]

[Formula 8]



[0010] The bases under the base presence of this invention are an organic base and an inorganic base, and are inorganic bases preferably, for example, a sodium hydride, a sodium methylate, and a t-butoxy potassium are mentioned.

[0011] To S bodies (I), although it is a grade mol theoretically, a reaction may advance also in the amount of catalysts, for example, 10 - 20 mol% is sufficient as the amount of the base used of this invention to (I).

[0012] A solvent inactive for a reaction about the solvent of this invention is desirable, for example, are benzene and toluene.

[0013] Temperature was applied about the reaction temperature of this invention, and it is [ direction ] good and reacts at 110-120 degrees C preferably.

[0014] Although it goes on about the reaction time of this invention for a short time, it reacts preferably for 2 to 3 hours.

[0015] It repeats several times that the crystallization conditions of this invention add and carry out the crystallization of the organic solvent to the hydrochloric-acid aqueous solution. By this, R (III) with more sufficient purity can be obtained.

[0016] The organic solvent of the crystallization conditions of this invention is a polar solvent, for example, are the ether and ethanol.

[0017] Racemization of the S bodies (I) of this invention can be carried out, and the technique of obtaining R bodies (III) can be recycled any number of times.

[0018] In order to perform the manufacture technique of this invention industrially, the following two technique is possible.

[0019] (1) Perform optical resolution after carrying out racemization, making transesterification perform in addition to the reaction mixture of N [ which is expressed with a formula (IV) in the solution which makes a principal component S bodies (I) or S bodies (I) ], and N'-dibenzyl piperazine-2-carboxylic-acid low-grade alkyl ester, and L-menthol.

[0020] (2) In addition to the diastereomer compound solution which the compound and L-menthol which are expressed with a formula (IV) in this solution are made to react, and was obtained, perform optical resolution simultaneously after heating and carrying out racemization of the S bodies (I).

[0021] It is recyclable any number of times as it stated the account of a front, when which technique was adopted above.

[0022] An example is given to below and this invention is explained to it in detail.

[0023]

[Example] (R) -1, synthetic :N [ of 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester ], and N'-dibenzyl piperazine-2-carboxylic-acid methyl-ester 36.7g (114mmol) was agitated, using toluene 100ml as a solvent, L-menthol 26.1g (167mmol) was added at the room temperature, heating reflux was performed for 30 minutes using the Dean Stark trap, and toluene was dehydrated. NaH(distributed object, 55 - 60%)1g (26mmol) was added after cooling a reaction mixture, and heating reflux was performed for 3 hours. At this time, 60ml toluene was distilled off and the \*\* methanol was performed by the technique of adding new toluene 60ml. 2N after cooling a reaction mixture HCl When 60ml and ether 150ml were added and churning was carried out at 20-25 degrees C for 1 hour, the crystal separated, and (R)-1 and 32.4g (diastereomer purity 65.8%d. ) of 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester-hydrochloride-hydrates were obtained by \*\*\*\*ing the crystal and drying.

[0024] Furthermore, it is 0.2N about this mixture. HCl 60ml, EtOH Recrystallization was performed by 100ml and, finally (R)-1 and 20.2g (35% [ of yield ] and diastereomer purity 98.8%d.e.) of 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester-hydrochloride-hydrates were obtained.

[0025] At this time, NaOH was extracted 3 times by toluene 30ml as optimum-dose \*\*\*\* and pH 12 28% to the filtrate of two obtained batches. Concentration hardening by drying of the organic layer was dried and carried out with magnesium sulfate, and it obtained oil 38.7g (R/S=2/7). Toluene 100ml was added to this oil, heating reflux was performed for 30 minutes using D an Stark, and toluene was dehydrated. NaH(distributed object, 55 - 60%)1g (26mmol) was added after cooling a reaction mixture, and heating reflux was performed for 3 hours. (When the reaction mixture was checked at this time, racemization was carried out to (R/S=1 / 1).) 2N By adding HCl60ml and ether 150ml, a crystal's separating, if it agitates at 20-25 degrees C for 1 hour, and \*\*\*\*ing the crystal, and drying (R) -1 and 17.6g (diastereomer purity 75.0%d.e.) of 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester-hydrochloride-hydrates were obtained.

[0026] Furthermore, it is 0.2N about this mixture. HCl 60ml, EtOH Recrystallization was performed by 100ml and, finally (R)-1 and 12.0g (21% [ of yield ] and diastereomer purity 96.1%d.e.) of 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester-hydrochloride-hydrates were obtained. Consequently, the total yield which added one racemization recycling improved with Y= 56.2% (32.2g).

[0027]

[Effect of the Invention] The manufacturing methods of this invention are optical activity (R)-1 [ useful as intermediate field of the drug of outstanding anti-\*\*\*\* and anti-Alzheimer's-disease medicine (JP,7-23387,A) ], and the industrially excellent manufacture technique which can manufacture efficiently 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester.

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[Translation done.]

## \*NOTICES\*

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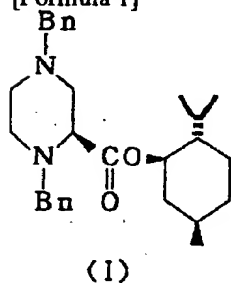
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## CLAIMS

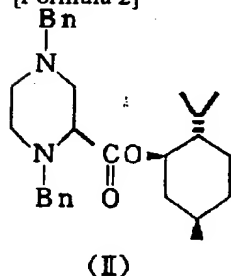
## [Claim(s)]

[Claim 1] The solution which makes a principal component (S)-1 expressed with a formula (I), 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester, or this ester is heated under base presence. After considering as (R)- expressed with a formula (II), (S)-1, and 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester mixture, (R)-1, the manufacture technique of 4-screw (phenyl methyl)-2-piperazine carboxylic-acid-L-menthyl ester which are expressed with the formula (III) characterized by carrying out optical resolution.

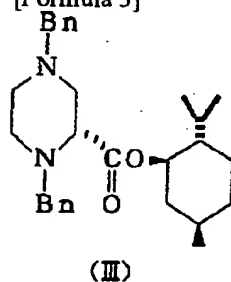
## [Formula 1]



## [Formula 2]



## [Formula 3]

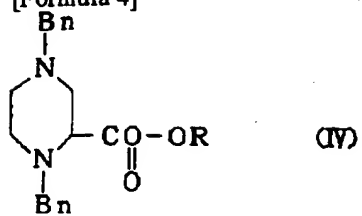


[Claim 2] The manufacture technique according to claim 1 of considering as the compound expressed with a formula (II), performing transesterification in addition to the reaction mixture of N [ which is expressed with a formula (IV) in the solution which makes a principal component the compound or this compound expressed with a formula (I) ], and N'-dibenzyl piperazine-2-carboxylic-acid low-grade alkyl ester, and L-menthol, and performing a chemistry split.

[Claim 3] The manufacture technique according to claim 1 which carries out optical resolution simultaneously in addition to the reaction mixture to which the transesterification of the compound and L-menthol which are expressed with a formula (IV) was made to perform after considering as the compound which heats the solution which makes a principal component the compound or this compound expressed with a formula (I) under base presence, and is expressed with a formula (II).

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[Formula 4]



(R shows a low-grade alkyl group among a formula.)

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[Translation done.]